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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,321	08/31/2006	Morten Reeslev	36731-000093/US	9441

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EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,321	REESLEV ET AL.	
	Examiner	Art Unit	
	PAUL C. MARTIN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-18,20-30,34,37-42,44,45 and 48-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-18,20-30,34,37-42,44,45 and 48-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13, 15-18, 20-30, 34, 37-42, 44, 45 and 48-60 are pending in this application and were examined on their merits.

Applicant's request for reconsideration (Pre-Appeal Brief Request for Review filed 05/13/2010) of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

The rejection of pending claims 1-13, 15-18, 20-30, 34, 37-42, 44, 45 and 48-58 under 35 U.S.C. § 103(a) as being unpatentable over Tuompo *et al.* (US 5,714,343) in view of Koumara *et al.* (US 5,591,554) is withdrawn in view of the New Rejections herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 is newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 requires the fluorescence in step d) of Claim 1 be measured directly on the liquid vehicle without interruption of contact between the liquid vehicle and the contaminants. It is unclear how fluorescence (presumably from soluble enzyme substrates) will be measured on the vehicle rather than in the vehicle. Further, as Claim 1 requires that the liquid vehicle be evacuated through the filter prior to measurement and the filter retains the contaminants, it is unclear how the liquid vehicle can remain in contact with the contaminants during the measurement step.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-13, 15-18, 20, 22-26, 34, 37, 39, 41, 42, 44, 45, 48-52, 54-60 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Koumura *et al.* (US 5,591,554).

Koumura *et al.* teaches a method for the detection of microorganisms wherein a liquid sample of viable microorganisms (bacteria and fungi such as the yeast *Saccharomyces,* etc (Column 3,Lines 36-38) or industrial food manufacturing waste water (Column 6, Lines 41-43 are contacted with methylumbelliferyl derivatives, such as 4-methumbelliferyl phosphate (4-MUP) (inherently the free acid and substrate for alkaline phosphatase) (Column 3, Lines 3-9) and incubated for 10 minutes to 6 hours (Column 3, Lines 50-53); wherein the microorganisms are incubated with peptone medium (non-selective growth enhancer) prior to the centrifugation step (Column 5, Lines 9-10); wherein after incubation insoluble residue such as microbial cells are removed by centrifugation (Column 3, Lines 54 and Column 6, Lines 49-50); and wherein the non-fluorescent enzyme substrate in the liquid vehicle forms fluorescent products upon hydrolysis by enzymes characteristic (expressed constitutively) to the microorganisms which are measured directly in the liquid vehicle and correlated to the amount and presence of bacteria in the sample in a linear relationship between the number of microorganisms and released 4-MU (Column 11, Claim 1 and Column 6, Table 2 and Column 8, Lines 15-17 and Fig. 1); and wherein the viscosity of the medium is reduced by dilution prior to the assay (Column 7, Lines 20-28).

It is inherent in the method of Komura *et al.* that the use of peptone as a non-selective growth-enhancer will increase the overall sensitivity in the detection step as the growth and multiplication of microbes will increase the amount of endogenous enzymes able to interact with the detectable enzyme substrate and increase the released signal (detectable moiety).

It is inherent in the method of Koumara *et al.* that the liquid vehicle containing the fluorescent substrates comprises multiple substrates providing signals that are combined into one measured signal value because the liquid vehicle contains multiple molecules of the fluorescent substrate 4-MUP which combine to give a total, measurable color formation, and that the amount of substrate does not limit the rate of production of the detectable moiety.

Koumura *et al.* does not teach a method wherein the sample is passed though a filter to concentrate the bacteria on the filter, contacting the influent side of the filter with a liquid vehicle containing a detectable enzyme substrate, allowing interaction between the substrate and bacteria on the filter, evacuating the liquid vehicle from the influent side of the filter to the effluent side by applying elevated pressure on the influent side of the filter or applying a lowered pressure on the effluent side of the filter prior to the detection of the detectable moiety; wherein the medium is air; wherein the medium is passed through a prefilter that dos not retain the bacteria; wherein the filter has a pore size of at most 20 μm and at least 0.1 μm;

wherein the detectable moiety is detectable in an amount of at most 100, 50, 20, 10 or 1 picomoles; or wherein several different known volumes of medium are passed though a filter to ensure that at least one of the volumes contains a suitable number of contaminants.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Komura *et al.* to use a filter to retain the microbes prior to contact with the detectable enzyme substrate because the centrifugation step performs an equivalent function to the use of a filter. In each method the liquid sample suspected of containing microbial contaminants is contacted with a detectable enzyme substrate, allowed to incubate and act on the substrate, the soluble fluorescent product of the action of endogenous characteristic microbial enzymes is separated from the microbial contaminants (either by filtration or by centrifugation) and then the fluorescence is measured and correlated to the amount and presence of microbial contaminants. It would have been obvious to one of ordinary skill in the art at the time of the instant invention that upon choosing to substitute the use of a filter in place of centrifugation that the filter have pores of sufficient size to retain the microbes of interest, but small enough to allow flow of the liquid medium so that the separation step can be accomplished.

The selection of filters with pores sizes of the claimed ranges would have been obvious as the result-effective adjustment of conventional working parameters (e.g., determining an appropriate filter pore size) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

It would have been obvious to one of ordinary skill in the art to effect the removal of the liquid medium from the contaminants by applying elevated pressure on the influent side of the filter or applying a lowered pressure on the effluent side of the filter prior to the detection of the detectable moiety because one of ordinary skill in the art would have understood that there are only a finite number of ways to separate a liquid from a solid; gravity (passive) or active (suction or pressure). One of ordinary skill in the art would have recognized that the active means would have been a more time-effective way to perform the separation step. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to pass several different known volumes of medium are passed though a filter to ensure that at least one of the volumes contains a suitable number of contaminants, because if a single volume did not contain enough measurable contaminants, the additive effect of multiple volumes will ensure that enough contaminants build up to be measured. It would have been obvious to one of ordinary skill in the art at the time of the instant invention that although Komura *et al.* is directed to the detection of microbes in liquid samples, the extension to the detection of airborne microbes would not be precluded from the method as long as the filter were sufficient to retain the microbes thereon.

Whether the microbes are air or liquid borne, as long as they are retained on the filter they can be assayed using the method of the reference. Further, the origin of the air sample to be assayed does not materially change the way the method works. Any sample of air can be assayed from any origin as long as any microbes therein are capable of being retained on the filter.

Those of ordinary skill in the art upon choosing to substitute filtration for centrifugation would have recognized the value of prefiltering liquid samples to remove large particulates which could adversely affect the assay from the medium prior to performing the method, especially in the case of industrial waste samples which could contain large rocks, wood, etc. Further, one of ordinary skill in the art would have recognized the advantageous property of detecting a contaminating microbe in the least amount possible, as obviously detecting a small amount of contamination is better than only detecting gross contamination. One of ordinary skill in the art at the time of the invention would have recognized that the result-effective adjustment of conventional working parameters (e.g., determining the least amount of detectable substrate released by microbial action) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Claims 1-6, 8-13, 15-18, 20-26, 34, 37, 39, 41, 42, 44, 45, 48-52, 54-60 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Koumura *et al.* (US 5,591,554) in view of Chen *et al.* (US 5,854,011).

The teachings of Koumura *et al.* were discussed above.

Koumura *et al.* does not teach wherein the substrate includes at least two substrates that produce detectable moieties providing distinguishable signals.

Chen *et al.* teaches that endogenous enzymes (such as phosphatase) in yeasts and molds have been identified which can hydrolyze chromogenic or fluorogenic substrates (such as the umbelliferyl substrates of Komura *et al.)* to produce a colored or fluorescent signal which can be detected visually or spectrophometrically (Column 2, Lines 40-63).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Komura *et al.* for the detection of microorganisms in a liquid sample using a single fluorescent enzyme substrate to use at least two substrates that produce distinguishable signals, such as a fluorescent and chromogenic substrate, because Chen *et al.* teaches that the endogenous enzymes in yeasts and molds (such as the *Saccharomyces* yeast taught by Komura *et al.*) are able to hydrolyze both fluorescent and chromogenic substrates.

One of ordinary skill in the art would have been motivated to make this modification because the use of multiple distinguishable substrates would allow the detection of more than one type of enzyme in a single sample. There would have been a reasonable expectation of success in making this modification because both methods are directed to the detection of microorganisms using detectable enzyme substrates.

Claims 1-13, 15-18, 20, 22-30, 34, 37, 39, 40, 41, 42, 44, 45 and 48-60 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Koumura *et al.* (US 5,591,554) in view of Tuompo *et al.* (US 5,714,343).

The teachings of Koumura *et al.* were discussed above.

Koumura *et al.* does not teach wherein the viscosity of the medium is reduced by means of treatment with a detergent; wherein the filter is part of a closed, sterile disposable filter device which integrates the filter and a filter housing into one irreversibly closed structural unit wherein the longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10 cm; or wherein the detection is performed in a microtiter system.

Tuompo *et al.* teaches a method for the detection of viable microorganisms (bacteria), the method comprising a) passing a known volume of liquid medium through a filter from influent side to effluent side in a closed, sterile filter device (Fig. 1) thereby concentrating and retaining microorganisms (bacteria) present on the filter device influent side, b) contacting the influent side of the filter with a liquid vehicle (test solution) containing a chromagenic enzyme substrate such as nitroblue tetrazolium (NBT) which forms a blue precipitate or soluble tetrazolium bromide (MTT) which forms a purple soluble stain; that through contact with constitutively expressed microbial dehydrogenase will produce a detectable moiety, and c) allowing the chromogenic substrate to interact with the microorganisms (bacteria) for a period of time wherein the interaction is not terminated and detecting the colored product retained on the filter and correlating the detection of the colored product to the presence of bacteria in the sample (Column 8, Claim 1 and Column 9, Claims 1, 2, 4, 5 and 7 and Column 4, Lines 66-67 and Column 5, Lines 1-25);

Tuompo *et al.* teaches wherein prior to step a) the medium is pre-filtered (Column 3, Lines 35-52), wherein the viscosity is reduced by means of dilution prior to step a) (Column 4, Lines 66-67) or treatment with a non-ionic detergent (Column 3, Lines 48-57) and wherein the detection is performed in a microtiter plate (Column 5, Lines 5-7).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Komura *et al.* for the detection of microorganisms in a liquid sample wherein a filtration step has been substituted for a centrifugation step as discussed above, with the close, sterile filter device as taught by Tuompo *et al.* above because a closed, sterile device would perform the separation step in an equivalent manner to a loose filter and would advantageously reduce possible sources of contamination from the filter itself.

While the reference does not teach the integration of the filter and filter housing into one irreversibly closed structural unit, wherein longest cross-sectional axis of the closed, sterile filter device does not exceed a length of 10 cm, those of ordinary skill in the art would have recognized that making the structure irreversibly closed and of a certain cross-sectional length are merely artisinal design modifications dependent upon personal preference and do not materially change the way the device functions. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Komura *et al.* to use the microtiter plate detection method as taught by Tuompo *et al.* because Komura *et al.* taught the use of multiple test tubes for performing the experiment on a plurality of medium dilutions and one of ordinary skill in the art would have recognized that the microtiter plate of Tuompo *et al.* would allow the experiment to be performed on a much larger scale and in a more efficient manner than using, for example 96 test tubes when a single small 96 well plate could be used.

There would have been a reasonable expectation of success in making these modifications because both methods are directed to the detection of liquid-borne microbial contaminants using detectable enzyme substrates.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
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06/25/2010

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